



OPINION ARTICLE

REVISED Effects of rapid recruitment and dissemination on Covid-19 mortality: the RECOVERY trial [version 2; peer review: 2 approved]

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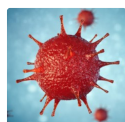
v2 First published: 21 Aug 2020, 9:1017
<https://doi.org/10.12688/f1000research.25842.1>
 Latest published: 23 Dec 2020, 9:1017
<https://doi.org/10.12688/f1000research.25842.2>

Abstract

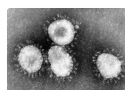
The RECOVERY trial is a large multi-armed, adaptive randomised controlled trial of treatments for Covid-19. It has rapidly recruited and demonstrated that hydroxychloroquine is ineffective in reducing mortality for hospitalised patients, whilst dexamethasone significantly reduces mortality among those patients using supplemental oxygen or on a ventilator. We estimate that the speed of recruitment and dissemination has probably decreased mortality in the UK by at least 200 hospitalised patients in the first month since the British Prime Minister announced the results. Despite its impressive speed, the trial only recruited about 10-15% of eligible patients, with recruitment rates ranging between 3% to 80% at participating hospitals. Had the trial recruited 50% of the eligible patients then our analysis suggests that more than 2,000 additional lives could have been saved. In a pandemic, rapid recruitment with high centre recruitment is absolutely essential to reduce deaths. Methods of improving site specific recruitment rates need investigating urgently.

Keywords

Covid-19, RECOVERY trial, recruitment



This article is included in the **Disease Outbreaks** gateway.



This article is included in the **Coronavirus** collection.

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 2		
(revision)		
23 Dec 2020	report	report
version 1		
21 Aug 2020		
	report	report

1. **Carlos Chaccour** , Instituto de Salud Global de Barcelona, Barcelona, Spain
 Universidad de Navarra, Pamplona, Spain
 Ifakara Health Institute, United Republic of Tanzania, Tanzania
2. **Heidi Gardner** , University of Aberdeen, Aberdeen, UK

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Knowlson C: Data Curation, Methodology, Validation, Writing – Review & Editing; Torgerson DJ: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Knowlson C and Torgerson DJ. **Effects of rapid recruitment and dissemination on Covid-19 mortality: the RECOVERY trial [version 2; peer review: 2 approved]** F1000Research 2020, 9:1017 <https://doi.org/10.12688/f1000research.25842.2>

First published: 21 Aug 2020, 9:1017 <https://doi.org/10.12688/f1000research.25842.1>

REVISED Amendments from Version 1

In response to the peer reviewers, we have made the following changes.

We have removed a repetitive sentence in the first paragraph of the methods and corrected a typo. In the discussion, we have included additional paragraphs to highlight the huge differences in recruitment rates between centres and noted it would be interesting to explore the reasons for this. We also note that the widespread of recruitment rates between centres is not unusual as it is our experience similar heterogeneity occurs in most clinical trials. We also note that despite the low recruitment proportion this does not seem to have introduced a biased sample as the proportion of participants from Black, Asian and minority ethnic groups are similar to the overall population, whilst the gender disparity is similar to the expected numbers of excess men as they are at higher risk than women. We include relevant references to support this. With respect to the finding of the negative outcomes for patients allocated to hydroxychloroquine we make this point, in a discussion paragraph, that our estimated health of benefit of the RECOVERY trial is conservative as it does not include cessation of inappropriate therapy for Covid-19. We include three more additional references to support these changes.

Any further responses from the reviewers can be found at the end of the article

Introduction

The RECOVERY randomised controlled trial (RCT) is a world-leading study of potential treatments for Covid-19 patients. It is large, simple, adaptive and multi-armed, allowing the investigators to test several treatments at the same time and quickly close trial arms if one of the treatments were found to be effective or ineffective. Importantly, this means the results can be rapidly disseminated to patients, clinicians and policy makers. The trial initially randomised Covid-19 patients admitted to hospital to one of five treatments: lopinavir-ritonavir (an HIV treatment); hydroxychloroquine; dexamethasone; azithromycin or usual care. The protocol was kept simple and flexible to allow “*a broad range of patients to be enrolled in large numbers*” (RECOVERY study protocol¹). Uniquely, the trial started recruiting nine days after submission of its protocol².

The trial has rapidly produced some key findings on the effectiveness and ineffectiveness of potential Covid-19 treatments. Its earliest, and somewhat overlooked, finding that hydroxychloroquine was ineffective (and probably harmful) to Covid-19 patients was important given that it has been widely promoted and used³. If the point estimate, of harm, in the hydroxychloroquine comparison is correct, then many lives will be saved worldwide by its, hopeful, reduction in use. Most recently the trial has demonstrated that lopinavir-ritonavir is also ineffective⁴. The most widely publicised finding from the RECOVERY trial, however, was that of the dexamethasone arm, which statistically significantly reduced mortality among Covid-19 patients at 28 days after randomisation³. This important result was demonstrated in less than three months after the trial was set-up. Within 81 days the trialists recruited 175 hospitals and enrolled 11,303 participants with 9,355 eligible for the dexamethasone comparison³. This remarkable trial will lead to many hundreds of

lives saved across the UK and the world and it is a tribute to the investigators and all those who took part either as participants, clinicians or researchers.

The RECOVERY trial is unique in its rapid recruitment and the speed at which it reported its first findings. Most trials, however, recruit relatively poorly and slowly, and therefore do not report their results in a timely fashion. RECOVERY did not recruit slowly but arguably it did recruit poorly. It has been reported that the overall recruitment rate to RECOVERY was 15%² of Covid-19 inpatients, with participating hospital recruitment ranging between 3% and 80% of eligible patients being recruited². In this respect, RECOVERY exhibited similar characteristics of the ‘typical’ non-Covid trial undertaken within an NHS setting: some recruitment sites enrol a very high proportion of eligible patients while others recruit relatively low numbers. Indeed, it is rare for all sites, or the majority, to consistently recruit a high proportion of eligible participants^{5,6}.

For the ‘standard’ trial (and for RECOVERY) to ensure rapid recruitment in the presence of poor average site recruitment, many more sites have to be enrolled in the study than would be required if there was high recruitment in all clinical sites, or recruitment of the target number takes longer than expected. However, if all sites could recruit the same proportion of eligible participants as the best recruiting site then trials would be finished more rapidly. This would have the benefits of reducing the overall cost of the trial and, most importantly, would improve patients’ health and save more lives. In ‘normal’ times this trade-off in lost lives and reduced quality of life, due to low recruitment, is not identified because either the data are not routinely collected (e.g., quality of life) or it is not collated so that it can be quantified. Slow or poor recruitment is even more catastrophic during a pandemic as there is a brief window of opportunity to recruit and complete a trial to enable infected patients to benefit from novel treatments. Therefore, whilst the clinical trials community in the UK has led the world in rapid, large and effective clinical trials to identify new treatments for Covid-19 there is still room for improvement. In this paper we look at the potential impact of the RECOVERY results on the numbers of patients surviving since the dexamethasone results were reported and then discuss the likely consequences of the RECOVERY trial’s ability to recruit only 15%² or less of the UK’s hospitalised Covid-19 patients into the trial.

Methods

First month mortality impact of RECOVERY results

To examine the actual impact of the RECOVERY trial on lives saved and its ‘potential’ impact had recruitment been even more swift, we used UK estimates of hospital admissions due to Covid-19⁷⁻¹⁰. We assumed that the proportion of patients that were eligible was the same as described in the RECOVERY trial, as well as the proportions on oxygen and ventilation. We used admissions data from the 16th June 2020 (date of the release of the trial results) until 15th July 2020. However, in line with the RECOVERY results we assumed that 24% of admitted patients did not need either oxygen or ventilator support so would not be offered the dexamethasone.

More rapid recruitment to the RECOVERY trial

The RECOVERY trial recruited 15% of patients with Covid-19 in UK hospitals. There was a huge variation in recruitment rates across the trial, which ranged from 3% to 80% of eligible participants. Recruitment started on the 19th March 2020 with rapid accrual of hospitals (132 participating hospitals by 3rd April) and by the 8th of June 2020 (with 175 hospitals open to recruitment), 11,303 patients had been randomised in total. Of these, 9,355 were randomised into the steroid comparison so this part of the study closed to recruitment³. Assuming an overall 15% recruitment rate, then this implies there were 75,353 patients with Covid-19 in UK hospitals during the recruitment period (although routine statistics suggest that there had been 114,935 Covid-19 admissions across the UK by this date⁷⁻¹⁰). Making the following assumptions we can estimate the possible loss of life by not recruiting a greater proportion of Covid-19 patients. In our following calculations we assume that on average 50% of eligible patients would take part in the RECOVERY trial if asked. Therefore, to enrol 11,303 patients then we would have to identify 22,606 patients admitted to NHS hospitals with COVID-19. We estimate this target would have been reached by the 1st April (as 24,978 COVID-19 patients had been admitted by this point⁷⁻¹⁰). The RECOVERY trial's preliminary results were released by the British Prime Minister eight days after recruitment was completed, which would have taken us to the 9th April 2020 (by which time 48,075 patients had been admitted to hospital in the UK). Between the 9th April 2020, when the results could have been available, and the 15th July 2020 there were 77,310 patients admitted with Covid-19⁷⁻¹⁰. To estimate the number of lives which could have been saved by the earlier completion of the dexamethasone arm, we made the following assumptions base on the RECOVERY trial results: that 83% of admitted patients had no contraindications to

dexamethasone, and that 24% of admitted patients did not need either oxygen or ventilator support so would not be offered the dexamethasone.

Results

In **Table 1** we show the estimated lives saved in this first month of dexamethasone being made available to all eligible patients (assuming that all hospitals implemented the guidelines without delay). In this month there were approximately 6,980 patients admitted to hospital with Covid-19, which equates to an estimated 5,793 patients who had no contraindications for dexamethasone treatment. **Table 1** shows that in just over a month more than 200 extra patients in the UK survived in hospital due to wider use of dexamethasone.

In **Table 2**, using the RECOVERY data we have estimated the potential benefit had all the participating hospitals recruited 50% of their eligible patients to RECOVERY (which should be achievable as clinical experience suggests that the vast majority of patients were happy to be included in the trial², although we are assuming there are no other large Covid-19 studies which would have caused competition for participants) and the dexamethasone recruitment was halted at 9,355 patients and the results were available by the 9th April.

The table shows that by not achieving the best recruitment which some UK hospitals are capable of means around 2,880 patients died unnecessarily.

Discussion

There is a need to complete and report all trials more quickly. This is especially the case in a pandemic. A reason why the RECOVERY trial could be done in the UK is due to the strong

Table 1. Estimated numbers of additional patients who survived up to 15th July due to RECOVERY.

Status	Proportion in each status as per RECOVERY Trial (Numbers admitted from 16 th June to 15 th July (6,980) of which 83% are eligible for dexamethasone) N = 5,793	Estimated deaths despite dexamethasone	Estimated deaths without dexamethasone
No Oxygen	24% (1,390)	14.0%* (195)	14.0% (195)
Oxygen alone	60% (3476)	22.0%** (765)	26.2% (911)
Ventilation	16% (927)	29.1%** (270)	41.4% (384)
Total deaths		1,230	1,490
Additional lives saved		260	

*Assumes steroids are not given to hospitalised but not oxygenated patients as per the results from the RECOVERY trial.

**Adjusted rather than observed differences between groups are used, which are 12.3 and 4.2% reduction in 28-day mortality for ventilated and oxygen supported patients, respectively.

Table 2. Estimated additional patients who survived up to 15th July with 50% recruitment to RECOVERY.

Status	Proportion in each status as per the RECOVERY Trial (Numbers admitted from 9 th April to 15 th July (77,310) of which 83% are eligible for dexamethasone) N = 64,167	Steroid deaths	Usual care deaths
No Oxygen	24% (15,400)	14.0%* (2,156)	14.0% (2,156)
Oxygen alone	60% (38,500)	22.0%** (8,470)	26.2% (10,087)
Ventilation	16% (10,267)	29.1%** (2,988)	41.4% (4,251)
Total deaths		13,614	16,494
Additional lives saved		2,880	

*Assumes steroids are not given to hospitalised but not oxygenated patients as per the results from the RECOVERY trial.

**Adjusted rather than observed differences between groups are used, which are 12.3 and 4.2% point reduction in 28-day mortality for ventilated and oxygen supported patients, respectively.

research infrastructure and having a national health service. However, we could do better. During the height of the pandemic, government advisors in the daily briefing encouraged patients and their doctors to take part in clinical trials. Whilst some hospitals recruited a remarkable 80% of eligible patients many did less well or did not take part². If some hospitals can recruit such high proportions of participants, then the majority should be able to do so. The differences in recruitment between sites is dramatic, and it would be interesting to find out why. If further information was released from the RECOVERY team, it could be determined whether there was a correlation between the number of COVID-19 admissions (and therefore reduced capacity of site teams) and poor recruitment. We understand that hospitals will be under more pressure than normal, especially when the number of cases are high, which may reduce their ability to recruit. We suspect that the reason for the disparity is unlikely to be this simple, as our experience, across a range of clinical areas, is that even before the pandemic trials have often had a disproportionate recruitment across sites. It would be beneficial to trial management teams to find out why some sites are more efficient at recruiting (such as a greater trust-wide emphasis on research) and whether this information can be used to transform low recruiting sites to reach their full potential. This remains a key area of research which should be explored in the future.

In addition to where the patients are being recruited to the RECOVERY trial, it is important to consider who are the patients taking part and whether there was any bias about who was approached. There was a difference between sexes taking part in the Dexamethasone comparison as 64% were men and 36% were women, however this fits with the finding that men are more likely to be seriously affected by COVID-19 and therefore more men are hospitalised with the condition¹¹. While the ethnicity of participants in the dexamethasone arm of the study was not published, those involved in the another

comparison of the RECOVERY trial, between lapanavir-ritonavir and usual care, were 15–18% Black, Asian and minority ethnic, compared with 74–77% White (the remaining 8% being unknown)¹², which fits with the ethnicity proportions in the UK¹³. The baseline characteristics therefore do not suggest a major disparity between the patients recruited and their distribution in the general population.

If there are no proven treatments available yet, we would argue that the best care for affected patients would be to offer participation in a study to help identify an effective treatment. If there is a second wave of the disease over the winter then measures need to be put into place to ensure that all eligible patients are offered the chance to take part in a clinical trial: swift action in recruitment will save more lives.

There has been some criticism of the RECOVERY trialists for reporting their results by press conference rather than in a peer reviewed journal². The peer-reviewed paper published in the *New England Journal of Medicine*³ on July 17th 2020 had only trivial differences from the basic data released on the 16th June 2020. Had the trialists waited for the peer reviewed paper to be published before having a press conference then it is likely over 200 patients in the UK would have died, plus many more internationally. Consequently, the rapid dissemination of results, in our view, was justified.

Whilst this paper has focused just on the dexamethasone results we must not forget the potentially harmful effects noted in the use of hydroxychloroquine¹⁴. Results from the RECOVERY trial showed the use of hydroxychloroquine led to a combined increase in mortality and ventilator use among hospitalised patients. Whilst ‘off label’ use of this drug for covid-19 is likely be small in the UK, the Food and Drug Administration (FDA) in the USA gave an emergency use authorisation for Covid-19 patients on the basis of little robust evidence¹⁵. This would have

led to widespread use in the USA. The RECOVERY trial's results are likely to have reduced the use of this drug and led to a reduction in mortality and morbidity, which is beyond the scope of this paper to estimate.

Conclusions

Rapid recruitment and dissemination in the RECOVERY trial has, we estimate, saved at least 200 lives in the UK in first month since the trial's results were released. However, we have estimated that the number lives saved, had the recruitment rate been at least 50% of eligible patients, would have been an order of magnitude greater.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Contributors

DT conceived the paper and wrote the first draft and CK revised and expanded the paper and identified data sources. Both authors contributed to the final approved manuscript. DT acts as the guarantor and affirms that the manuscript is an honest and transparent account of the study.

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Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 04 January 2021

<https://doi.org/10.5256/f1000research.31480.r76357>

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The authors have addressed my minor comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Internal medicine, Infectious diseases, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 04 January 2021

<https://doi.org/10.5256/f1000research.31480.r76358>

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Heidi Gardner 

Health Services Research Unit, University of Aberdeen, Aberdeen, UK

Thank you for making revisions to this article based on my feedback, it's a great piece of work and one that I'm looking forward to seeing built upon in the future.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical trials methodology, participant recruitment, mixed methods research, inclusivity in trials, trial efficiency

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 December 2020

<https://doi.org/10.5256/f1000research.28519.r74832>

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Heidi Gardner 

Health Services Research Unit, University of Aberdeen, Aberdeen, UK

Thank you for requesting that I review this interesting and very timely article. I enjoyed reading this, as usual from these authors the manuscript is well written, robustly reported, and refreshingly concise.

The range of recruitment rates from 3% to 80% was shocking to me, and I'd like to see more detail in this if possible. Are the authors able to break these rates down to individual hospitals or health boards? I'd be interested to know if the low recruiters had high rates of COVID and vice versa to see if there's a correlation. More broadly this information could provide insights into how various sites view trials - are they a priority? If not, why not? If so, what's contributing to that culture and how can we replicate it in other sites?

The other thing that I feel is lacking in this paper is discussion around WHO the participants are. Recruiting is all well and good, but if RECOVERY recruited only white British people and no minorities, then that's clearly a problem - particularly given the disparities around the impact of COVID on different ethnic minority groups in our society. The fact that RECOVERY doesn't appear to have collected data on the ethnicity of participants is problematic, and deserves a comment here.

The implications of this work are potentially wide-ranging, and have got me thinking about what research area(s) should be focused on to ensure that the day-to-day usual trials that are run in the UK are as effective (and quick) as they can be. I'd like to see what the authors think about this. Should we be thinking about engagement with the public, involvement of public and patient partners, research into how the option to take part in a trial could potentially be a part of routine care? The fact that patients have died as a result of poor recruitment in RECOVERY is a fantastic starting point for discussion - the numbers are stark, but what to do with them now?

Overall, this is an important and thought-provoking article, and one that should act as a wake-up call to those of us working to improve trials. There is much work to be done in this area.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical trials methodology, participant recruitment, mixed methods research, inclusivity in trials, trial efficiency

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 15 Dec 2020

David Torgerson, University of York, UK, York, UK

With respect to the second reviewer (Heidi Gardener) we very much agree with you that it would be interesting to find out what the differences were between the participating hospitals that caused the wide range in recruitment rate, as this would be incredibly valuable for current and future trials. Unfortunately, as we are not involved in the RECOVERY trial we do not have access to data broken down by site to determine whether there is a correlation between poor recruitment and the number of covid admissions. You have definitely touched upon an interesting area for consideration, around how different sites view trials. Although this was outside the scope of this study, it is certainly something we would be interested in researching in the future.

You brought up another excellent point about who the participants are that participated in the trial. In two of the three published RECOVERY papers these data are not reported. However, one of the papers does report the proportion of participants from ethnic minorities and we have updated the paper to include a section on this in the discussion, which as far as we can see there does not seem to be a disparity. However, unfortunately we are unable to look at BAME admission rates across the participating sites to know for sure if there is any disparity as we do not have access to these data. Again, this is a potential area of future research if the RECOVERY team can provide this information.

It would be fantastic if we could improve recruitment rates at those sites which do not deliver to target. We think that there is unlikely to be a single factor that is involved, and it will very much depend on individual sites and reasons may change over time too (e.g. site capacity, competing studies, Principal Investigator engagement). Indeed, we hope that the increased media attention on clinical trials recently will encourage more patients to seek participation in trials, however we think that the biggest effect would be at a site level as we believe that all patients should be given the opportunity to take part in a trial.

We have addressed these issues in the updated version of our paper.

Competing Interests: No competing interests were disclosed.

Reviewer Report 27 November 2020

<https://doi.org/10.5256/f1000research.28519.r74833>

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In this opinion piece, Knowlson and Torgerson analyze the recruitment rate and recruitment success of the RECOVERY trial. They point to a large variation between sites ranging from 15 to 80% of all eligible patients and argue that a much faster completion of the trial was feasible if all sites had recruited at least 50% of eligible patients. The authors then proceed to estimate the lives lost due to poor recruitment delaying trial completion. This analysis is based on the proven efficacy of dexamethasone.

The opinion piece is indeed provoking and well thought. The introduction is well written and sets the stage appropriately. The methods and assumptions are described at large and the results mostly support the conclusion.

As an opinion piece, I think it could further improve by mentioning other potential causes for slow/poor recruitment, such as whether hydroxychloroquine, azithromycin or any of the RECOVERY interventions were used outside the trial.

The authors make clear that their conclusion is based on the effect of dexamethasone and I think this sufficiently illustrates the point. However, as much as RECOVERY served to support the scale-up of dexamethasone, it served to reduce the compassionate use of hydroxychloroquine which often comes with additional risk of harms. Additional consideration could be given to the lives

saved by a reduction in the use of hydroxychloroquine.

Minor:

- There is a zero missing in the phrase: "from the 16th June 2020 (date of the release of the trial results) until 15th July 202:".
- The assumption: "83% of patients without contraindications and 24% not needing oxygen or ICU" is mentioned twice.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Internal medicine, Infectious diseases, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 15 Dec 2020

David Torgerson, University of York, UK, York, UK

With respect to the first reviewer (Carlos Chaccour) we have undertaken the minor corrections he suggested in his review. We have also added an additional paragraph in the discussion regarding the point he made about the impact of the RECOVERY findings on off label hydroxychloroquine use, which, worldwide, would also have an impact on reducing harm. We include this in our updated version of the paper.

Competing Interests: None

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